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Relationship between Resonance Energy per π-Electron and Carcinogenicity in Arenes

TERUO KURIHARA[1], NOBORU MOTOHASHI[2], ATSUSHI SHIMIZU[3], GUI LIN PANG[4] and JOSEPH MOLNÁR[5]

[1]*Department of Chemistry, Faculty of Science, Josai University, 1-1 Keyakidai, Sakado-shi, Saitama 350-02 Japan;*
[2]*Department of Medicinal Chemistry, Meiji College of Pharmacy, 1-22-1 Yato-cho, Tanashi-shi, Tokyo 188 Japan;*
[3]*Nittai Kashiwa High School, 224 Tobari, Kashiwa-shi, Chiba 350-02 Japan;*
[4]*Department of Chemical Engineering, Xinjiang Institute of Technology, Urumqi, Xinjiang, 830008 People's Republic of China;*
[5]*Faculty of Medicine, Institute of Microbiology, Albert Szent-Györgyi Medical University, Szeged, Dóm tér 10, H-6720 Hungary*

Abstract. *The resonance energy per π-electron of various arenes was calculated using Aihara's TRE theory. There seemed to be a correlation between the resonance energy valume per π-electron of the cation species (lacking a carbon atom) with the highest approximate superdelocalizability ($Sr^{r}(E)$) from the parent skeleton and carcinogenicity, i.e. the induction of cancer by arenes (three-ring, four-ring, five-ring, six-ring and seven-ring) seems to be dependent on the resonance energy per π-electron in they contain.*

Some physical and chemical mechanisms have a role in the chemical carcinogenesis. A particular compound can bind to a cell and induce carcinogenesis via conformational changes (1,2), which are generated in different ways after the release of carcinogens which were previously bound to nucleotide bases. Recently we have reported the effect of the relationship between resonance energy (RE) and resonance energy per π-electron (REPE) on benz[*c*]acridines and benzo[*a*]phenothiazines. The mechanism involved in the induction of the antibacterial and antiplasmid effects of arenes seems to be different from the method involved in its antitumor and carcinogenic effects (3). π-Electron distribution in the 1-benzene ring might be responsible for the induction of anticancer activity (4). Similarly, a correlation has been found between electrochemical oxydation-reduction potentials of substituted benz[*c*]acridine, and carcinogenicity (5,6). Energy was accumulated in the K-region of the molecular orbitals (7). In our recent experiments, the compounds were investigated for a structure-activity relationship by computer programs and the possible relationship between electronic structure and carcinogenicity will be further analyzed.

Correspondence to: Dr. Noboru Motohashi, Department of Medicinal Chemistry, Meiji College of Pharmacy, 1-22-1 Yato-cho, Tanashi-shi, Tokyo 188 Japan. Tel: (+) 0424-21-0412; FAX: (+)0424-21-1489

Key Words: Arenes, REPE, $Sr^{r}(E)$.

Calculations

The electronic distribution was calculated by the Hükel molecular orbital method (HMO). The reactivity indices used for comparing the carcinogenicity were the frontier electron theory and the approximate superdelo-calizability of the carbon atom. Resonance energy per π-electron of arenes was calculated by Aihara's graph theory of aromaticity (8,9). For these calculations, the FACOM M770 computer in the Josai University Information Sciences Center was used.

Results and Discussion

The resonance energies per π-electron (REPEs) of arenes (**1-47**) and both of their analogs (**1P1-47P1, 1P2-47P2**) which lack a double bond at the position of the largest and the second largest bond-order in the parent skeleton, and the cationic species which lack a carbon atom with the largest $Sr^{r}(E)$ in the parent skeleton were calculated by Aihara's topological resonance energy (TRE).

Calculation of REPE on arenes. Table I shows the bond-

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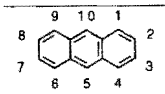
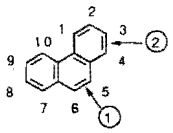
Table I. *Bond-order, REPEs and $Sr^{r(E)}$ of three-ring arenes (1,2).*

Compound's number and structure	Bond[1]	Bond order (ß unit)[2]	REPE (in ß unit)			Approximate superdelocalizability (in ß unit)			Carcinogenicity index[9]
			REPE(P)[3]	REPE(P1)[4]	REPE(P2)[5]	Position[6]	$Sr^{r(E)}$ [7]	REPE ($Sr^{r(E)}$)[8]	
	1,2	0.737	0.0339	0.0307	-	5	0.934	0.0319	+
1, anthracene									
	5,6 3,4	0.775 0.707	0.0390	0.0418	0.0309	5	0.569	0.0298	-
2, phenanthrene									

[1]Bond: Position with the biggest bond-order.
[2]Bond-order: Bond-order (in ß unit) at the position with the biggest bond-order.
[3]REPE (P): Resonance energy per π-electron (in ß unit) of parent.
[4]REPE (P1): REPE except the position of the biggest bond-order in parent.
[5]REPE (P2): REPE except the position of the 2nd big bond-order in parent.
[6]Position: Position with the biggest approximate superdelocalizability in parent.
[7]$Sr^{r(E)}$: Approximate superdelocalizability in parent.
[8]REPE ($Sr^{r(E)}$): REPE except the position of the biggest $Sr^{r(E)}$ in parent.
[9]Carcinogenicity index: +: carcinogenic; -: noncarcinogenic. Ref. 10.

Table II. *Bond-order, REPEs and $Sr^{r(E)}$ of four-ring arenes (3-8).*

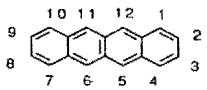
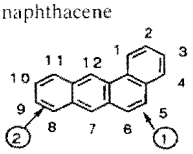
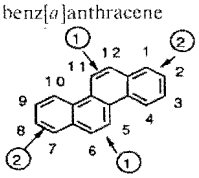
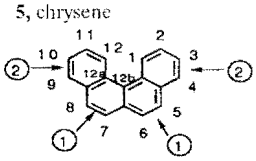
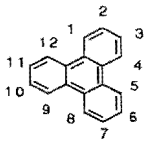
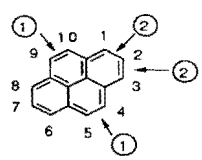
Compound's number and structure	Bond[1]	Bond order (ß unit)[2]	REPE (in ß unit)			Approximate superdelocalizability (in ß unit)			Carcinogenicity index[9]
			REPE(P)[3]	REPE(P1)[4]	REPE(P2)[5]	Position[6]	$Sr^{r(E)}$ [7]	REPE ($Sr^{r(E)}$)[8]	
	1,2	0.741	0.0307	0.0285	-	5	0.999	0.0311	-
3, naphthacene									
	5,6 8,9	0.783 0.732	0.0357	0.0387	0.0328	7	0.976	0.0322	++
4, benz[*a*]anthracene									
	5,6 1,2	0.754 0.712	0.0382	0.0387	0.0329	6	0.572	0.0312	±
5, chrysene									
	5,6 3,4	0,761 0.712	0.0381	0.0387	0.0329	12b	0.505	0.0267	-, ++
6, benzo[*c*]phenanthrene									
	1,2	0.690	0.0411	0.0332	-	1	0.324	0.0295	-
7, triphenylene									
	4,5 1,2	0.777 0.669	0.0374	0.0390	0.0265	1	0.610	0.0265	-

Table III. *Bond-order, REPEs and* $Sr^{(E)}$ *of five-ring arenes (9-23).*

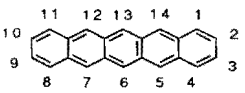
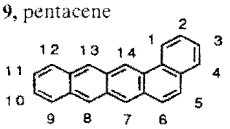
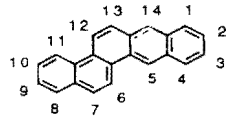
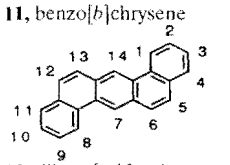
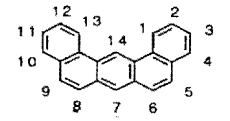
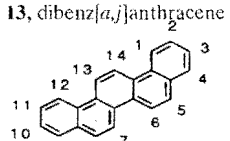
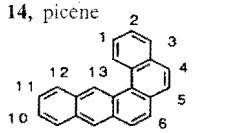
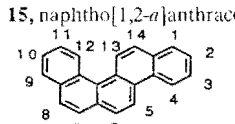
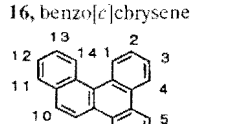
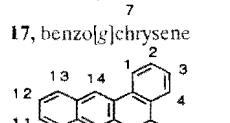
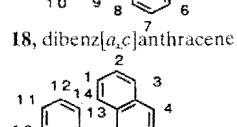
Compound's number and structure	Bond[1]	Bond order (ß unit)[2]	REPE (in ß unit)			Approximate superdelocalizability (in ß unit)			Carcinogenicity index[9]
			REPE(P)[3]	REPE(P1)[4]	REPE(P2)[5]	Position[6]	$Sr^{(E)}$ [7]	REPE $(Sr^{(E)})$[8]	
 **9,** pentacene	1,2	0.742	0.0286	0.0267	-	6	1.286	0.0307	-
 **10,** benzo[*a*]naphthacene	5,6 9.10	0.785 0.739	0.0330	0.0353	0.0312	8	0.975	0.0324	-
 **11,** benzo[*b*]chrysene	12,13 6,7	0.764 0.748	0.0355	0.0368	0.0353	14	0.819	0.0329	+
 **12,** dibenz[*a,h*]anthracene	5,6 2,3	0.778 0.703	0.0367	0.0388	0.0313	7	0.573	0.0315	+
 **13,** dibenz[*a,j*]anthracene	5,6 3.4	0.780 0.703	0.0366	0.0387	0.0313	7	0.833	0.0323	+
 **14,** picene	5,6 13,14	0.758 0.732	0.0379	0.0388	0.0368	5	0.480	0.0320	-
 **15,** naphtho[1,2-*a*]anthracene	6,7 4,5	0.772 0.756	0.0354	0.0368	0.0352	8	0.805	0.0328	+
 **16,** benzo[*c*]chrysene	7,8 13,14	0.766 0.761	0.0379	0.0387	0.0387	14	0.562	0.0318	+
 **17,** benzo[*g*]chrysene	9,10 11,12	0.746 0.716	0.0395	0.0389	0.0359	10	0.544	0.0334	+
 **18,** dibenz[*a,c*]anthracene	10,11 1,2	0.727 0.686	0.0384	0.0358	0.0315	9	0.716	0.0336	+
 **19,** dibenz[*c,g*]phenanthrene	4,5 6,7	0.765 0.746	0.0378	0.0387	0.0369	4	0.472	0.0313	-

Table III. *Bond-order, REPEs and $Sr^{\cdot(E)}$ of five-ring arenes (**9-23**).*

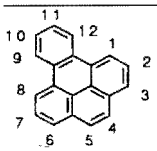
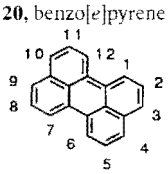
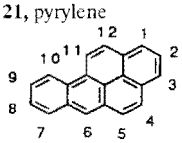
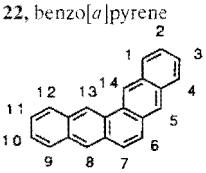
Compound's number and structure	Bond[1)]	Bond order (ß unit)[2)]	REPE (in ß unit)			Approximate superdelocalizability (in ß unit)			Carcinogenicity index[9)]
			REPE(P)[3)]	REPE(P1)[4)]	REPE(P2)[5)]	Position[6)]	$Sr^{\cdot(E)}$ [7)]	REPE ($Sr^{\cdot(E)}$)[8)]	
 **20**, benzo[*e*]pyrene	4,5 9,10	0.775 0.689	0.0395	0.0411	0.0324	3	0.515	0.0313	-
 **21**, pyrylene	2,3	0.707	0.0370	0.0340	-	3	0.621	0.0313	-
 **22**, benzo[*a*]pyrene	4,5 11,12	0.784 0.754	0.0362	0.0382	0.0357	6	1.015	0.0351	+
 **23**, pentaphene	6,7 3,4	0.790 0.729	0.0339	0.0368	0.0311	5	0.642	0.0304	-

Table IV. *Bond-order, REPEs and $Sr^{\cdot(E)}$ of six-ring arenes (**24-40**).*

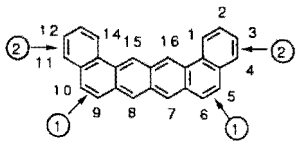
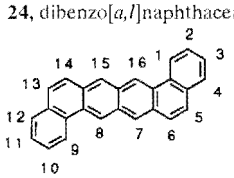
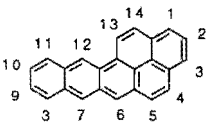
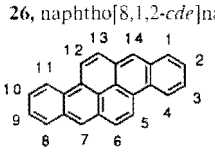
Compound's number and structure	Bond[1)]	Bond order (ß unit)[2)]	REPE (in ß unit)			Approximate superdelocalizability (in ß unit)			Carcinogenicity index[9)]
			REPE(P)[3)]	REPE(P1)[4)]	REPE(P2)[5)]	Position[6)]	$Sr^{\cdot(E)}$ [7)]	REPE ($Sr^{\cdot(E)}$)[8)]	
 **24**, dibenzo[*a,l*]naphthacene	5,6 3,4	0.784 0.699	0.0344	0.0364	0.0295	7	0.865	0.0326	+
 **25**, dibenzo[*a,j*]naphthacene	5,6 3,4	0.784 0.699	0.0344	0.0364	0.0295	7	0.790	0.0325	+
 **26**, naphtho[8,1,2-*cde*]naphthacene	4,5 13,14	0.785 0.747	0.0339	0.0355	0.0330	6	1.054	0.0339	+
 **27**, dibenzo[*a,h*]pyrene	5,6 1,2	0.762 0.724	0.0352	0.0355	0.0322	7	1.070	0.0353	+

Table IV. *Bond-order, REPEs and* $Sr^{r}(E)$ *of six-ring arenes (**24-40**).*

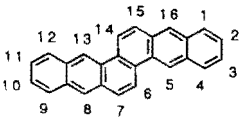
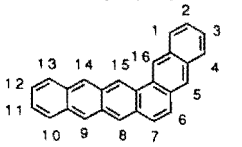
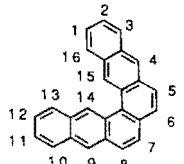
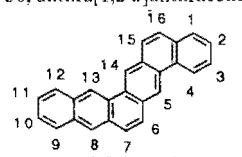
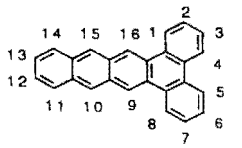
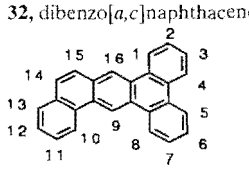
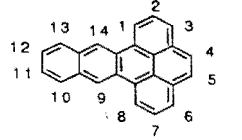
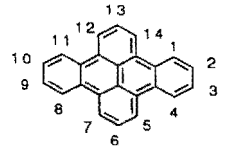
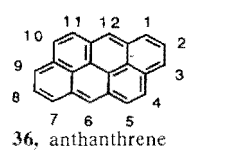
(continued 1) Compounds number and structure	Bond[1]	Bond order (ß unit)[2]	REPE (in ß unit) REPE(P)[3]	REPE(P1)[4]	REPE(P2)[5]	Approximate superdelocalizability (in ß unit) Position[6]	$Sr^{r}(E)$ [7]	REPE $(Sr^{r}(E))$[8]	Carcinogenicity index[9]
 **28,** dibenzo[*b,k*]chrysene	6,7 1,2	0.0758 0.734	0.0336	0.0343	0.0316	8	0.597	0.0313	-
 **29,** hexaphene	6,7 10,11	0.790 0.738	0.0319	0.0343	0.0302	9	0.965	0.0310	-
 **30,** anthra[1,2-*a*]anthracene	5,6 2,3	0.767 0.734	0.0335	0.0342	0.0316	14	0.617	0.0310	-
 **31,** benzo[*c*]pentaphen	6,7 15,16	0.785 0.776	0.0349	0.0372	0.0364	8	0.727	0.0320	-
 **32,** dibenzo[*a,c*]naphthacene	11,12 1,2	0.738 0.685	0.0357	0.0344	0.0297	10	0.926	0.0348	+
 **33,** tribenzo[*a,c,j*]anthracene	14,15 12,13	0.776 0.704	0.0386	0.0403	0.0345	16	0.573	0.0335	-
 **34,** dibenzo[*de,qr*]naphthacene	4,5 10,11	0.775 0.726	0.0374	0.0384	0.0350	9	0.721	0.0332	+
 **35,** dibenzo[*fg,op*]naphthacene	1,2 5,6	0.690 0.667	0.0410	0.0353	0.0349	5	0.418	0.0324	-
 **36,** anthanthrene	4,5 1,2	0.784 0.689	0.0348	0.0362	0.0307	6	0.972	0.0344	+

Table IV. *Bond-order, REPEs and Sr' (E) of six-ring arenes (**24-40**).*

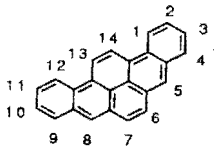
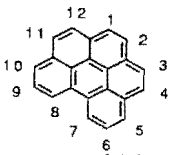
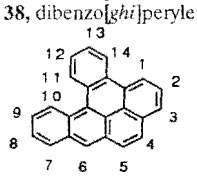
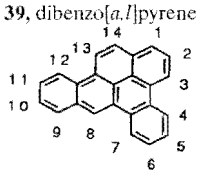
(continued 2) Compound's number and structure	Bond[1]	Bond order (ß unit)[2]	REPE (in ß unit)			Approximate superdelocalizability (in ß unit)			Carcinogenicity index[9]
			REPE(P)[3]	REPE(P1)[4]	REPE(P2)[5]	Position[6]	Sr'(E) 7]	REPE (Sr'(E)$_j$)8]	
 **37,** dibenzo[*ai*]pyrene	6,7 13,14	0.788 0.731	0.0359	0.0379	0.0339	5	0.973	0.0351	+
 **38,** dibenzo[*ghi*]perylene	3,4 1,2	0.765 0.734	0.0388	0.0395	0.0370	5	0.538	0.0318	-
 **39,** dibenzo[*a,l*]pyrene	4,5 7,8	0.783 0.725	0.0376	0.0395	0.0350	6	0.975	0.0357	+
 **40,** dibenzo[*a,e*]pyrene	13,14 9,10	0.754 0.717	0.0385	0.0384	0.0351	8	0.821	0.0353	+

Table V. *Bond-order, REPEs and Sr' (E) of seven-ring arenes (**41-47**).*

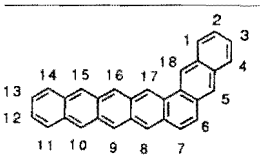
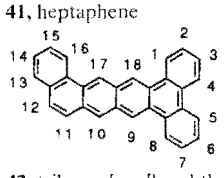
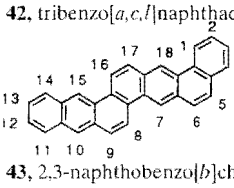
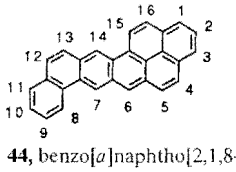
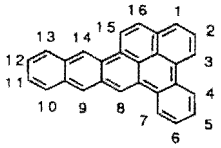
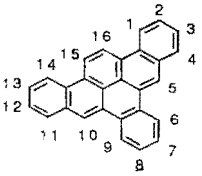
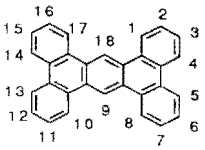
Compound's number and structure	Bond[1]	Bond order (ß unit)[2]	REPE (in ß unit)			Approximate superdelocalizability (in ß unit)			Carcinogenicity index[9]
			REPE(P)[3]	REPE(P1)[4]	REPE(P2)[5]	Position[6]	Sr'(E) 7]	REPE (Sr'(E)$_j$)8]	
 **41,** heptaphene	6,7 11,12	0.790 0.741	0.0302	0.0322	0.0289	9	1.170	0.0303	-
 **42,** tribenzo[*a,c,l*]naphthacene	11,12 13,14	0.783 0.700	0.0366	0.0384	0.0326	10	0.835	0.0346	-
 **43,** 2,3-naphthobenzo[*b*]chrysene	5,6 8,9	0.780 0.760	0.0346	0.0361	0.0354	10	0.654	0.0326	-
 **44,** benzo[*a*]naphtho[2,1,8-*hij*]naphthacene	4,5 12,13	0.783 0.779	0.0350	0.0364	0.0368	6	0.974	0.0346	+

Table V. *Bond-order, REPEs and Sr'$^{(E)}$ of seven-ring arenes (41-47).*

(continued 1) Compound's number and structure	Bond[1]	Bond order (ß unit)[2]	REPE (in ß unit) REPE(P)[3]	REPE(P1)[4]	REPE(P2)[5]	Approximate superdelocalizability (in ß unit) Position[6]	Sr'$^{(E)}$ 7)	REPE (Sr'$^{(E)}$)[8]	Carcinogenicity index[9]
	15,16	0.747	0.0363	0.0357	0.0347	9	0.849	0.0345	+
	10,11	0.734							
45, benzo[*a*]naphtho[8,1,2-*cde*]naphthacene									
	15,16	0.731	0.0381	0.0367	0.0348	5	0.753	0.0352	+
	3,4	0.714							
46, tribenzo[*a,c,i*]pyrene									
	1,2	0.689	0.0400	0.0354	0.0353	9	0.528	0.0343	+
	3,4	0.689							
47, tetrabenzo[*a,c,h,j*]anthracene									

order, resonance energy per π-electron (REPE) and approximate superdelocalizability REPE(Sr'$^{(E)}$) of three-ring arenes (**1,2**), which have 14 π-electrons. From the energy calculations for REPE(P), it was suggested that phenanthrene (**2**) is more stable than anthracene (**1**). The value of REPE(Sr'$^{(E)}$) (0.0319ß) for carcinogenic anthracene (**1**) was higher than REPE(Sr'$^{(E)}$) (0.0298ß) for noncarcinogenic phenanthrene (**2**). This is only a comparison of two three-ring arenes (**1,2**) but, it the appear that a higher value than 0.0319ß of REPE(Sr'$^{(E)}$) is necessary for three-ring arenes to become carcinogenic (Table I)(10).

Table II shows the bond-order, resonance energy per π-electron (REPE) and approximate superdelocalizability (Sr'$^{(E)}$) of four-ring arenes (**3-8**), which have 18 π-electrons. The values of REPE(P) led us to suggest that triphenylene (**7**) is the most stable structure of the 6 four-ring arenes (**3-8**). The REPE(Sr'$^{(E)}$) of carcinogenic benz[*a*]anthracene (**4**) was 0.0322ß, and the values of the noncarcinogenic four-ring arenes were 0.0265ß-0.0312ß (**3,5-8**). This comparison of 6 four-ring arenes (**3-8**) suggests that the greater values than 0.0322ß are essential for carcinogenicity in four-ring arenes (Table II).

Table III shows the bond-order, resonance energy per π-electron (REPE) and approximate superdelocalizability (Sr'$^{(E)}$) of five-ring arenes (**9-23**), which have 22 π-electrons. Higher REPE(Sr'$^{(E)}$) values than 0.0315ß for five-ring arenes are needed for the appearance of carcinogenicity. The values of the REPE(Sr'$^{(E)}$) of the 8 carcinogenic five-ring arenes are; benzo[*b*]chrysene (**11**, REPE(Sr'$^{(E)}$): 0.0329ß), dibenz[*a,h*]anthracene (**12**, REPE(Sr'$^{(E)}$): 0.0315ß), dibenz[*a,j*]anthracene (**13**, REPE(Sr'$^{(E)}$): 0.0323ß), naphtho[1,2-*a*]anthracene (**15**, REPE(Sr'$^{(E)}$): 0.0328ß), benzo[*c*]chrysene (**16**, REPE(Sr'$^{(E)}$): 0.0318ß), benzo[*g*]chrysene (**17**, REPE(Sr'$^{(E)}$): 0.0334ß), dibenz[*a,c*]anthracene (**18**, REPE(Sr'$^{(E)}$): 0.0336ß) and benzo[*a*]pyrene (**22**, REPE(Sr'$^{(E)}$): 0.0351ß). All of which were greater values than the case for the non-carcinogenic compounds. The REPE(Sr'$^{(E)}$) values of the 5 noncarcinogenic five-ring arenes were; pentacene (**9**, REPE(Sr'$^{(E)}$): 0.0307ß), dibenzo[*c,g*]phenanthrene (**19**, REPE(Sr'$^{(E)}$): 0.0313ß), benzo[*e*]pyrene (**20**, REPE(Sr'$^{(E)}$): 0.0313ß), pyrylene (**21**, REPE(Sr'$^{(E)}$): 0.0313ß) and pentaphene (**23**, REPE(Sr'$^{(E)}$): 0.0304ß). The two noncarcinogenic five-ring arenes of benzo[*a*]naphthacene (**10**) with a value of 0.0324ß and picene (**14**) with a value of 0.0320ß were exceptions. It can be stated that the carcinogenicity of five-ring arenes (**9-23**) is correlated with the higher values than REPE(Sr'$^{(E)}$) 0.0315ß. Noncarcinogenic five-ring arenes (**10** and **14**) are exceptions to the role (Table III).

Table IV shows the bond-order, resonance energy per π-electron (REPE) and approximate superdelocalizability (Sr'$^{(E)}$) of six-ring arenes (**24-40**), which have 26 π-electrons. The values of REPE(Sr'$^{(E)}$) suggest that a higher REPE(Sr'$^{(E)}$) than 0.0332ß for six-ring arenes (except for tribenzo[*a,c,j*]anthracene (**33**)) is required for the appearance of carcinogenicity. The stability of the REPE(Sr'$^{(E)}$) values of 9 carcinogenic six-ring arenes *e.g.* dibenzo[*a,l*]naphthacene (**24**, REPE(Sr'$^{(E)}$): 0.0326ß), dibenzo[*a,j*]naphthacene (**25**,

REPE($Sr'^{(E)}$): 0.0325ß), naphtho[8,1,2-*cde*]naphthacene (**26**, REPE($Sr'^{(E)}$): 0.0339ß), dibenzo[*a,h*]pyrene (**27**, REPE($Sr'^{(E)}$): 0.0353ß), dibenzo[*a,c*]naphthacene (**32**, REPE($Sr'^{(E)}$): 0.0348ß), dibenzo[*de,qr*]naphthacene (**34**, REPE($Sr'^{(E)}$): 0.0332ß), anthanthrene (**36**, REPE($Sr'^{(E)}$): 0.0344ß), dibenzo[*a,i*]pyrene (**37**, REPE($Sr'^{(E)}$): 0.0351ß), dibenzo[*a,l*]pyrene (**39**, REPE($Sr'^{(E)}$): 0.0357ß) and dibenzo[*a,e*]pyrene (**40**, REPE($Sr'^{(E)}$): 0.0353ß) (except noncarcinogenic tribenz[*a,c,j*]anthracene (**33**) with 0.0335ß) were higher than the REPE($Sr'^{(E)}$) values of the 6 noncarcinogenic six-ring arenes. The values for noncarcinogenic compounds were dibenzo[*b,k*]chrysene (**28**, REPE($Sr'^{(E)}$): 0.0313ß), hexaphene (**29**, REPE($Sr'^{(E)}$): 0.0310ß), anthra[1,2-*a*]anthracene (**30**, REPE($Sr'^{(E)}$): 0.0310ß), benzo[*c*]pentaphene (**31**, REPE($Sr'^{(E)}$): 0.0320ß), dibenzo[*fg,op*]naphthacene (**35**, REPE($Sr'^{(E)}$): 0.0324ß), and benzo[*ghi*]perylene (**38**, REPE($Sr'^{(E)}$): 0.0318ß) (Table IV).

Tables V shows the bond-order, resonance energy per π-electron (REPE) and approximate superdelocalizability ($Sr'^{(E)}$) of seven-ring arenes (**41-47**), which have 30 π-electrons. The values of REPE($Sr'^{(E)}$) imply that carcinogenicity can be deduced from REPE($Sr'^{(E)}$) values are greater than 0.0343ß in the case of seven-ring arenes. The exception was tribenzo[*a,c,l*]naphthacene (**42**). The REPE($Sr'^{(E)}$) values of the 4 carcinogenic seven-ring arenes are benzo[*a*]naphtho[2,1,8-*hij*]naphthacene (**44**, 0.0346ß), benzo[*a*]naphtho[8,1,2-*cde*]naphthacene (**45**, 0.0345ß), tribenzo[*a,e,i*]pyrene (**46**, 0.0352ß), and tetrabenzo[*a,c,h,j*]anthracene (**47**, 0.0343ß). The noncarcinogenic tribenzo[*a,c,l*]naphthacene (**42**) with a value of 0.0346ß was an exception. The two noncarcinogenic seven-ring arenes heptaphene (**41**) with 0.0303ß and 2,3-naphthobenzo[*b*]chrysene (**43**) with 0.0326ß had relatively low REPE($Sr'^{(E)}$) values (Table V).

In general it can be concluded that higher REPE($Sr'^{(E)}$) values may be responsible for the carcinogenicity of arenes.

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